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Human albumin for adults with sepsis

An updated systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Sepsis affects millions of people and imposes a substantial economic and social burden worldwide. However, the role of human albumin in the management of septic patients remains unclear.

Methods: EMBASE, PubMed, and Cochrane Library databases were searched. Randomized controlled trials regarding the use of human albumin in septic patients were eligible. The overall mortality and the intensive care unit (ICU), in-hospital/28-day, and 90-day mortality were pooled, respectively. Subgroup analyses were performed according to target population, type and dose of human albumin, and type of control group. Risk ratios (RRs) was calculated.

Results: Twenty-four randomized controlled trials were finally included. Meta-analysis showed that human albumin cannot decrease the overall (RR = 1.02, *P* = .56), ICU (RR = 1.06, *P* = .65), in-hospital/28-day (RR = 1.01, *P* = .68), and 90-day (RR = 1.01, *P* = .65) mortality of total patients. Subgroup analyses showed that human albumin both cannot significantly decrease the overall, ICU, in-hospital/28-day, and 90-day mortality of sepsis and septic patients. Additionally, 20% human albumin (RR = 0.89, *P* = .03) and high daily dose of human albumin (RR = 0.90, *P* = .03) might benefit for the survival of patients with septic shock.

Conclusions: Based on the current evidence, the general use of human albumin to improve the survival of septic patients cannot be recommended.

Abbreviations: CI = confidence interval, ICU = intensive care unit, MAP = mean arterial pressure, RCT = randomized controlled trial, RR = risk ratio, TSA = trial sequential analysis.

Keywords: albumin, meta-analysis, mortality, sepsis, septic shock

1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] According to data from the Global Burden of Diseases, in 2017 alone, 48.9 million incident cases of sepsis worldwide, resulting 11.0 million sepsis-related deaths, which accounted for 19.7% of all global deaths that year.[2] Recognizing the urgency, the World Health Organization declared that the improvement of sepsis prevention, recognition, and treatment is a global health priority.[3] Despite advancements in medical research and clinical practices over the past 3 decades, sepsis still affects millions of people with a mortality exceeding 20%.[2,4] Thus, the identification and validation of appropriate management of sepsis are crucial for the improving outcomes in septic patients.

Human albumin, a common colloid, is frequently used in the resuscitation of patients with sepsis. Beyond its oncotic properties, human albumin offers potential benefits through various non-oncotic functions,[5] including inflammation factors clearance, antioxidant effects, immunomodulation, capillary permeability, hemostatic effect, and endothelial stabilization.[6–8] Numerous randomized controlled trials (RCTs) have been conducted to explore the role of human albumin in septic patients, but the conclusions were controversial.[9–13] However, many differences exist among these RCTs, primarily involving control group, type of human albumin, and duration of follow-up, which may lead to the inconsistent conclusions. Additionally, several meta-analyses on this topic have produced and the results were also contradictory due to the heterogeneity of number of included RCTs and studies designs.[14–16] In summary, the

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role of human albumin in the management of septic patients remains unclear and the last international guidelines only give recommendations of human albumin to patients who received large volumes of crystalloids over using crystalloids alone.[4,17] Current guidelines cannot provide an aggressive using strategy of human albumin due to the lack of proven benefit and higher cost of albumin compared to crystalloids, thereby confusing the use of human albumin in septic patients among the clinical practice.

We conducted an updated and comprehensive systematic review and meta-analysis of previous RCTs and attempted to clarify the effect of human albumin on the survival of septic patients and further explored the potential influence factors of efficacy of human albumin.

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2. Methods

2.1. Registration

The current study was registered in the PROSPERO and the registration number was CRD42023471215. It was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[18] Given that it involved a systematic review and meta-analysis of published data, ethical approval was not applicable.

2.2. Literature search

EMBASE, PubMed, and Cochrane Library databases were searched from the earliest available publication until March 21, 2024. Search items were: ((sepsis [All Fields]) OR (septic shock [All Fields])) AND ((albumin [All Fields]) OR (colloid [All Fields])) AND ((randomized [All Fields]) OR (randomized [All Fields]) OR (clinical trial [All Fields])).

2.3. Selection criteria

Two independent investigators (ZB and YL) screened literature. RCTs would be eligible, if they explored the efficacy of human albumin infusion in patients with sepsis or septic shock. Exclusion criteria were as follows: (1) duplicates; (2) guidelines, reviews, or meta-analyses; (3) case reports, comments, or letters; (4) experimental or animal studies; (5) studies where patient without sepsis or septic shocks; (6) studies where human albumin treatment was not given; (8) non-randomized studies; (9) protocol of studies; (10) patients' age < 18 years; (11) retracted studies; and (12) mortality data cannot be extracted.

2.4. Data extraction

Two independent investigators (ZB and YL) extracted the following information from each study: first author, publication year, country, number of centers, population, sample size, number of patients with sepsis, number of patients with septic shock, type and daily dose of human albumin, duration of albumin, age, percent of male, baseline serum albumin level, mean arterial pressure (MAP), type of control group, number of patients in albumin and control groups, follow-up duration, and number of deaths. Disagreement was resolved by discussing with another investigator (YX). If some data was not available, we contacted with the corresponding authors and attempt to obtain the relevant data.

2.5. Outcomes and definitions

The primary outcome should be the overall mortality and the secondary outcomes including the intensive care unit (ICU), 28-day, and 90-day mortality. Age > 60 years[19] would be considered, if mean/median age was >60 years in both groups. Otherwise, age < 60 years would be considered. MAP > 60 mm Hg[20] would be considered, if mean/median MAP was >60 mm Hg in both groups. Otherwise, MAP < 60 years would be considered. The average daily dose of human albumin (g/kg) would be calculated based on each trial's published data and categorized by 0.5 g/kg.[21] If weight data were lacking, the average weight of the subjects would be assumed to be 70 kg.

2.6. Quality assessment

The Cochrane Risk of Bias tool[22] was used to assess the risk of bias, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Risk of bias graph and summary were performed.

2.7. Statistical analysis

A random-effect model was employed to the current meta-analysis. Dichotomous outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). P value < .05 was considered statistically significant. Cochrane Q test and the I^2 statistics were employed to assess the heterogeneity, and P-value < .1 or I^2 > 50% was considered as a statistically significant heterogeneity. When there were ≥10 studies included, the publication bias was assessed by Egger tests, and P-value < .1 was considered as a significant publication bias.[23,24] As for the primary and secondary outcomes, subgroup analyses were performed according to target population (i.e., sepsis and septic shock), age (i.e., >60 and <60 years), type of human albumin (i.e., 0.1%, 0.25%. 1%, 4%, 5%, and 20% human albumin), type of control group (i.e., colloid and crystalloid), baseline MAP (i.e., >60 and <60 mm Hg), and dose of human albumin (i.e., >0.5 and <0.5 g/kg). This meta-analysis was performed by the Review Manager software version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and R software (version 4.0.3, R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Trial sequential analysis (TSA) was performed to evaluate type I error risk and to calculate the required information size or number of patients required to determine if the results of this meta-analysis can be considered conclusive or if further studies should be conducted.[25] This involved calculating the diversity adjusted required information size, creating a cumulative Z-curve, and establishing trial sequential monitoring and futility boundaries.[26] Risk of type I error was maintained at 5% with a power of 80%. Baseline (control group) mortality and a clinically meaningful anticipated relative mortality reduction of 10% was used based on the lowest and most conservative value from power calculations presented for included trials investigating a primary mortality endpoint.[9,10] TSA was performed by the TSA Viewer version 0.9.5.10 Beta. (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, 2016, Copenhagen, Denmark). The Grading of Recommendations Assessment, Development and Evaluation system[27] was employed to assess the quality of the evidence from our meta-analysis.

3. Results

3.1. Study selection

Overall, 3452 papers were identified from the 3 electronic databases and 1 study was identified by manual retrieval. Finally, 24 RCTs were included in the meta-analysis[9–13,28–46] (Fig. 1). Among them, the sample size ranged from 15 to 2314, and the publication years were between 1983 and 2022. Twenty-three

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RCTs were published as full texts[9–13,28–40,42–46] and 1 was published as abstract.[41] Three RCTs were performed in Italy,[10,30,37] 2 in USA,[12,28] 2 in India,[11,46] 2 in Germany,[36,39] 2 in France,[41,43] 2 in Brazil,[32,45] 1 in Austria,[35] 1 in Czech Republic,[40] 1 in South Africa,[29] 1 in Spain,[34] 1 in Turkey,[31] 1 in Iran,[44] and 5 in 2 or more countries.[9,13,33,38,42] The characteristics of studies were summarized in Table 1. Target population included single patients with sepsis in 6 RCTs,[30,32,35,40,43,44] single patients with septic shock in 8 RCTs,[11–13,28,29,41,42,46] and patients with sepsis or septic shock in 10 RCTs.[9,10,31,33,34,36–39,45] Twenty RCTs provided the concentration of human albumin.[9–13,28,30,32–37,39–41,43–46] Type of human albumin included 0.1%, 0.25%, 1%, 4%, 5%, and 20% human albumin. The characteristics of patients were summarized in Table S1, Supplemental Digital Content, http://links.lww.com/MD/O233 The infusion strategies of human albumin were summarized in Table S2, Supplemental Digital Content, http://links.lww.com/MD/O233 The definitions of sepsis/septic shock of included studies were summarized in Table S3, Supplemental Digital Content, http://links.lww.com/MD/O233.

3.2. Quality assessment

For the random sequence generation, 17 RCTs had low risk of bias.[9–11,13,33–43,45,46] For the allocation concealment, 16 RCTs had low risk of bias.[9–11,13,33–36,38–43,45,46] For the blinding of participants and personnel, 10 RCTs had low risk of bias.[9,13,29,30,33–35,38,39,45] For the blinding of outcome assessment, 15 RCTs had low risk of bias.[9,12,13,28–30,33–35,38–42,45] For the incomplete outcome data, 22 RCTs had low risk of bias.[9–13,28–30,32–45] For the selective reporting, 23 RCTs had low risk of bias.[9–13,28–30,32–46] For other bias, 9 RCTs had low risk of bias.[11,13,29,33,38,39,41,42,45] Five RCTs had low risk of bias for all domains[13,33,38,39,45] (Fig. S1, Supplemental Digital Content, http://links.lww.com/MD/O232).

3.3. Meta-analysis

3.3.1. Overall population.

3.3.1.1. Overall analysis. Twenty-four RCTs explored the effect of human albumin on the mortality (n = 10,876). Meta-analysis showed that human albumin cannot decrease the overall mortality (RR = 1.02, 95%CI = 0.96–1.07, P = .56) (Fig. 2). The heterogeneity (I^2 = 8%, P = .35) and publication bias (P = .18) were not significant among these studies. TSA indicated that the diversity adjusted information size was 6000 which was less than that in our study (n = 10,876) and the cumulative Z-curve surpassed the futility boundary, but it did not cross the trial sequential monitoring boundary for benefit or harm, indicating further studies are not required as they are unlikely to change the current conclusion (whether benefit or harm) (Fig. S2, Supplemental Digital Content, http://links.lww.com/MD/O232). Additionally, human albumin also cannot decrease the ICU (RR = 1.06, 95%CI = 0.83–1.34, P = .65), in-hospital/28-day (RR = 1.01, 95%CI = 0.96–1.07, P = .68), and 90-day (RR = 1.01, 95%CI = 0.96–1.08, P = .65) mortality and none of them exhibited significant heterogeneity (Table 2).

3.3.1.2. Subgroup analysis based on the type of human albumin. One RCT's type of human albumin was 0.1% human albumin[39] (n = 624), 1 was 0.25%[13] (n = 1869), 2 were 1%[33,35] (n = 2347), 2 were 4%[9,45](n = 1578), 7 were 5%[11,12,28,30,32,34,36] (n = 692), and 7 were 20%[10,37,40,41,43,44,46] (n = 2995). Meta-analysis showed that human albumin infusion cannot decrease the overall

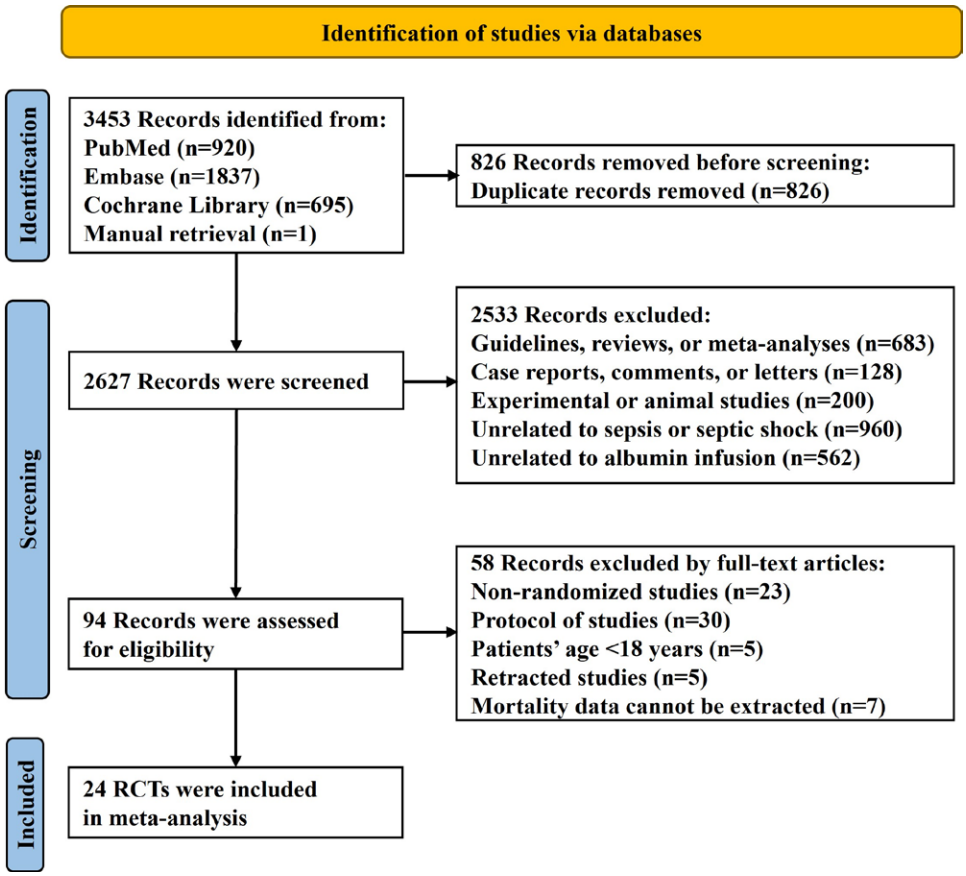
Identification of studies via databases
Identification
3453 Records identified from:
PubMed (n=920)
Embase (n=1837)
Cochrane Library (n=695)
Manual retrieval (n=1)
826 Records removed before screening:
Duplicate records removed (n=826)
Screening
2627 Records were screened
2533 Records excluded:
Guidelines, reviews, or meta-analyses (n=683)
Case reports, comments, or letters (n=128)
Experimental or animal studies (n=200)
Unrelated to sepsis or septic shock (n=960)
Unrelated to albumin infusion (n=562)
94 Records were assessed for eligibility
58 Records excluded by full-text articles:
Non-randomized studies (n=23)
Protocol of studies (n=30)
Patients' age <18 years (n=5)
Retracted studies (n=5)
Mortality data cannot be extracted (n=7)
Included
24 RCTs were included in meta-analysis

Figure 1. Flow chart of study selection. RCT = randomized controlled trial.

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Table 1

Characteristics of included randomized controlled trails.

First author (year)	Country	No. centers	Sample size	Population	No. sepsis	No. septic shock	Albumin group	Control group
Rackow (1983)[28]	USA	1	18	Septic shock	0	18	5% human albumin	6% hetastarch 0.9% saline
Aitchison (1985)[29]	South Africa	1	34	Septic shock	0	34	human albumin	Human anti-lipopolysaccharide-specific globulin
Rackow (1989)[12]	USA	1	20	Septic shock	0	20	5% human albumin	10% pentastarch
Dominioni (1991)[30]	Italy	4	62	Sepsis	62	0	5% human albumin	Immunoglobulin G
Abraham (1998)[13]	USA and Canada	105	1879	Septic shock	0	1879	0.25% human albumin	Monoclonal antibody to human tumor necrosis factor
Yakut (1998)[31]	Turkey	1	40	Sepsis and septic shock	NA	NA	human albumin	Immunoglobulin G
Fernandes (2001)[32]	Brazil	1	15	Sepsis	15	0	5% human albumin	Red blood cell
Warren (2001)[33]	19 countries	211	2314	Sepsis and septic shock	1203	1111	1% of human albumin	Antithrombin III
Rodríguez (2005)[34]	Spain	7	56	Sepsis and septic shock	36	20	5% human albumin	Polyvalent IgM-enriched Ig
Gonano (2006)[35]	Austria	1	33	Sepsis	33	0	1% human albumin	Antithrombin
Hentrich (2006)[36]	Germany	6	206	Sepsis and septic shock	148	58	5% human albumin	IgMA-enriched immunoglobulin
Rice (2006)[38]	USA and Canada	19	81	Sepsis and septic shock	14	67	human albumin	Polyclonal ovine anti-TNF fragment antigen binding fragments
Palumbo (2006)[37]	Italy	1	20	Sepsis and septic shock	16	4	20% human albumin	6% hydroxyethyl starch
Werdan (2007)[39]	Germany	23	624	Sepsis and septic shock	162	462	0.1% human albumin	Immunoglobulin G
Dolecek (2009)[40]	Czech Republic	1	56	Sepsis	56	0	20% human albumin	6% hydroxyethyl starch
Charpentier (2011)[41]	France	29	798	Septic shock	0	798	20% human albumin	Normal saline
SAFE Study Investigators (2011)[9]	Australia and New Zealand	16	1218	Sepsis and septic shock	780	438	4% human albumin	Normal saline
Annane (2013)[42]	4 countries	57	616	Septic shock	0	616	4%, 5%, 20%, 25% human albumin	Isotonic saline
Caironi (2014)[10]	Italy	100	1810	Sepsis and septic shock	675	1135	20% human albumin plus crystalloid	Crystalloid alone
Thévenot (2015)[43]	France	25	191	Sepsis	191	0	20% human albumin and antibiotics	Antibiotics alone
Kakaei (2017)[44]	Iran	1	20	Sepsis	20	0	20% human albumin plus crystalloid	Crystalloid alone
Park (2019)[45]	Brazil	1	360	Sepsis and septic shock	165	195	4% human albumin and lactated Ringer	Lactated Ringer solution alone
Philips (2021)[11]	India	1	308	Septic shock	0	308	5% human albumin	Normal saline
Maiwall (2022)[46]	India	1	100	Septic shock	0	100	20% human albumin	Plasmalyte

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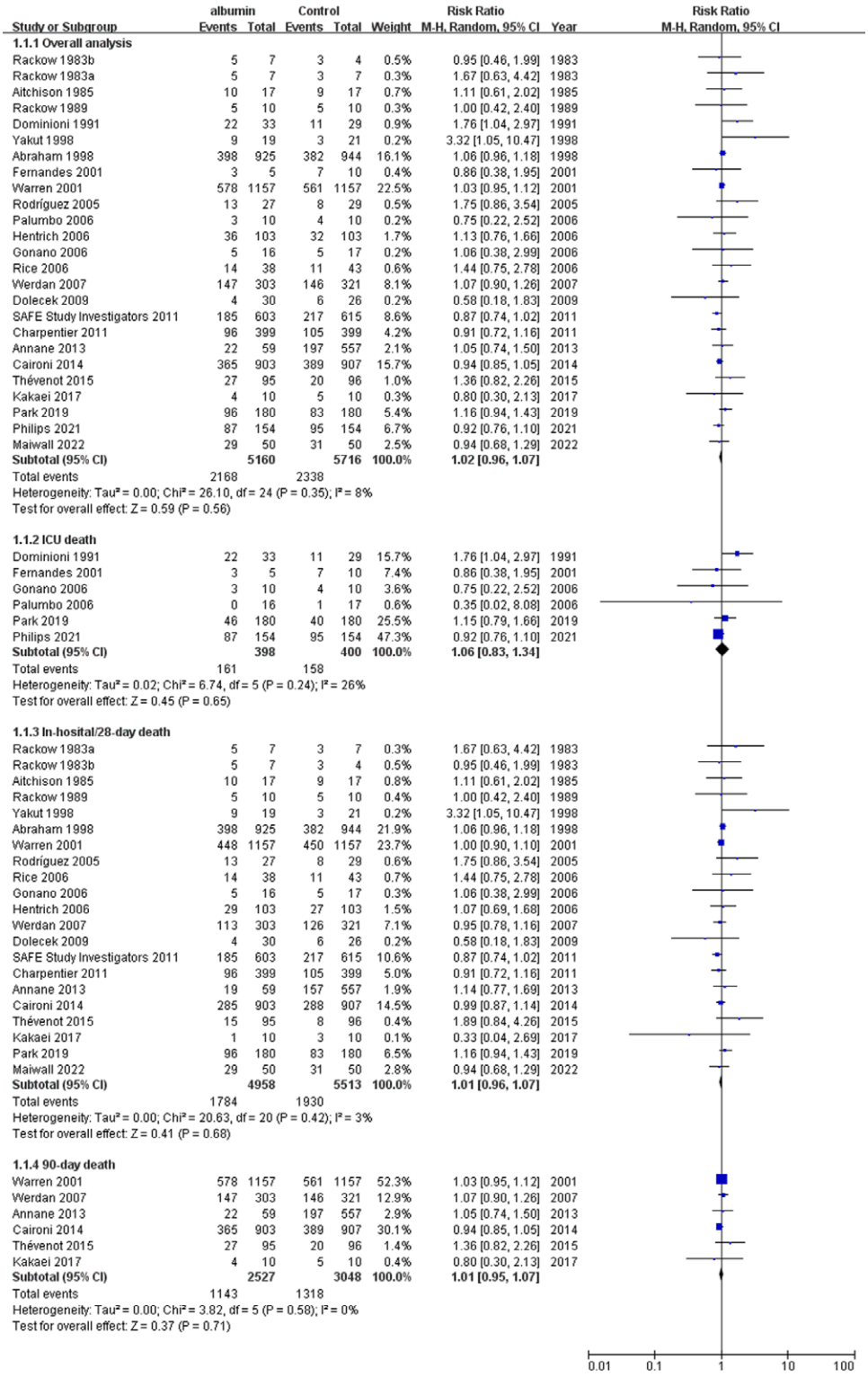

Figure 2. Forest plot showing the effect of human albumin treatment on overall, ICU, in-hospital/28-day, and 90-day mortality in total patients. ICU = intensive care unit.

mortality regardless of the type of human albumin used: 0.1% (RR = 1.07, 95%CI = 0.90–1.26, $P = .45$), 0.25% (RR = 1.06, 95%CI = 0.96–1.18, $P = .26$), 1% (RR = 1.03, 95%CI = 0.95–1.12, $P = .48$), 4% (RR = 0.99, 95%CI = 0.75–1.32, $P = .97$), 5% (RR = 1.12, 95%CI = 0.91–1.38, $P = .30$), or 20% (RR = 0.94, 95%CI = 0.86–1.03, $P = .22$), respectively (Table 2). The interaction was not statistically significant among the 6 subgroups ($I^2 = 0\%$, $P = .50$).

3.3.1.3. Subgroup analysis based on the dose of human albumin. Eleven RCTs explored the effect of low dose of human albumin on the mortality (n = 5602)[11,13,29,30,32–36,38,39] and 10 RCTs explored the high dose (n = 4598).[9,10,12,28,40,41,43–46]

Table 2

Subgroup analyses of the effect of human albumin on the mortality.

Category		Groups	No. studies	Effect estimate			Heterogeneity		Publication bias (Egger test)
				RR	95% CI	*P*	I^2	*P*	
Total patients									
Type of human albumin	0.1% albumin	*Overall analysis*	**1**	**1.07**	**0.90–1.26**	**.45**	\	\	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	1	0.95	0.78–1.16	.62	\	\	\
		90-day death	1	1.07	0.90–1.26	.45	\	\	\
	0.25% albumin	*Overall analysis*	**1**	**1.06**	**0.96–1.18**	**.26**	\	\	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	1	1.06	0.96–1.18	.26	\	\	\
		90-day death	\	\	\	\	\	\	\
	1% albumin	*Overall analysis*	**2**	**1.03**	**0.95–1.12**	**.48**	0%	.95	\
		ICU death	1	0.35	0.02–8.08	.51	\	\	\
		In-hospital/28-day death	2	1.00	0.90–1.10	.94	0%	.90	\
		90-day death	1	1.03	0.95–1.12	.48	\	\	\
	4% albumin	*Overall analysis*	**2**	**0.99**	**0.75–1.32**	**.97**	78%	.03	\
		ICU death	0	\	\	\	\	\	\
		In-hospital/28-day death	2	0.99	0.75–1.32	.97	78%	.03	\
		90-day death	0	\	\	\	\	\	\
	5% albumin	*Overall analysis*	**8**	**1.12**	**0.91–1.38**	**.30**	24%	.24	\
		ICU death	3	1.11	0.70–1.74	.66	63%	.07	\
		In-hospital/28-day death	5	1.19	0.88–1.60	.26	0%	.68	\
		90-day death	\	\	\	\	\	\	\
	20% albumin	*Overall analysis*	**7**	**0.94**	**0.86–1.03**	**.22**	0%	.80	\
		ICU death	1	0.75	0.22–2.52	.64	\	\	\
		In-hospital/28-day death	5	0.94	0.76–1.18	.61	12%	.33	\
		90-day death	3	0.97	0.84–1.12	.66	5%	.35	\
Dose of human albumin	<0.5g/kg	*Overall analysis*	**11**	**1.05**	**0.99–1.11**	**.11**	0%	.50	0.14
		ICU death	4	1.06	0.73–1.55	.75	47%	.13	\
		In-hospital/28-day death	8	1.03	0.96–1.10	.41	0%	.71	\
		90-day death	2	1.04	0.96–1.12	.33	0%	.71	\
	>0.5g/kg	*Overall analysis*	**10**	**0.96**	**0.89–1.03**	**.23**	0%	.55	0.55
		ICU death	1	1.15	0.79–1.66	.46	\	\	\
		In-hospital/28-day death	11	0.98	0.89–1.07	.59	5%	.40	0.82
		90-day death	3	0.97	0.84–1.12	.66	5%	.35	\
Type of control group	Other colloid	*Overall analysis*	**15**	**1.06**	**1.00–1.13**	*.04*	0%	.51	0.11
		ICU death	4	1.20	0.72–2.00	.49	19%	.29	\
		In-hospital/28-day death	12	1.03	0.97–1.10	.34	0%	.49	0.13
		90-day death	2	1.04	0.96–1.12	.33	0%	.71	\
	Crystalloid	*Overall analysis*	**10**	**0.95**	**0.89–1.02**	**.16**	0%	.61	0.42
		ICU death	2	0.97	0.79–1.19	.79	21%	.26	\
		In-hospital/28-day death	9	0.98	0.90–1.08	.73	13%	.33	\
		90-day death	4	0.96	0.87–1.07	.48	0%	.50	\
Age	<60-year	*Overall analysis*	**13**	**1.03**	**0.98–1.09**	**.23**	0%	.90	0.83
		ICU death	3	0.91	0.76–1.09	.31	0%	.79	\
		In-hospital/28-day death	11	1.02	0.96–1.09	.53	0%	.72	0.97
		90-day death	4	1.04	0.97–1.12	.27	0%	.68	\
	>60-year	*Overall analysis*	**9**	**1.02**	**0.89–1.16**	**.78**	42%	.09	\
		ICU death	2	1.36	0.90–2.06	.14	42%	.19	\
		In-hospital/28-day death	8	0.99	0.89–1.10	.87	19%	.28	\
		90-day death	1	0.94	0.85–1.05	.29	32%	.15	\
MAP	<60 mm Hg	*Overall analysis*	**2**	**0.92**	**0.78–1.08**	**.31**	0%	.91	\
		ICU death	1	0.92	0.76–1.10	.35	\	\	\
		In-hospital/28-day death	1	0.94	0.68–1.29	.68	\	\	\
		90-day death	\	\	\	\	\	\	\
	>60 mm Hg	*Overall analysis*	**10**	**0.99**	**0.92–1.07**	**.82**	4%	.40	0.24
		ICU death	3	1.08	0.77–1.51	.65	0%	.63	\
		In-hospital/28-day death	9	1.00	0.91–1.11	.98	17%	.29	\
		90-day death	3	1.01	0.89–1.15	.87	36%	.21	\

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Table 2

(***Continued***)

Category		Groups	No. studies	Effect estimate			Heterogeneity		Publication bias (Egger test)
				RR	95% CI	*P*	I^2	*P*	
Sepsis patients									
Type of human albumin	0.1% albumin	*Overall analysis*	\	\	\	\	\	\	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	\	\	\	\	\	\	\
		90-day death	\	\	\	\	\	\	\
	0.25% albumin	*Overall analysis*	**1**	**1.06**	**0.96–1.18**	**.26**	\	\	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	1	1.06	0.96–1.18	.26	\	\	\
		90-day death	\	\	\	\	\	\	\
	1% albumin	*Overall analysis*	**2**	**1.02**	**0.87–1.19**	**.84**	0%	.93	\
		ICU death	1	0.35	0.02–8.08	.51	\	\	\
		In-hospital/28-day death	2	1.02	0.87–1.19	.84	0%	.93	\
		90-day death	\	\	\	\	\	\	\
	4% albumin	*Overall analysis*	**2**	**0.88**	**0.72–1.08**	**.22**	0%	.87	\
		ICU death	1	0.84	0.42–1.66	.61	\	\	\
		In-hospital/28-day death	1	0.89	0.72–1.09	.26	\	\	\
		90-day death	\	\	\	\	\	\	\
	5% albumin	*Overall analysis*	**4**	**1.31**	**0.80–2.16**	**.29**	39%	.18	\
		ICU death	2	1.32	0.66–2.65	.44	53%	.14	\
		In-hospital/28-day death	2	1.76	0.35–8.95	.49	61%	.11	\
		90-day death	\	\	\	\	\	\	\
	20% albumin	*Overall analysis*	**4**	**1.16**	**0.96–1.40**	**.12**	0%	.50	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	3	0.91	0.32–2.55	.86	52%	.12	\
		90-day death	3	1.19	0.98–1.43	.08	0%	.63	\
Dose of human albumin	<0.5g/kg	*Overall analysis*	**6**	**1.13**	**0.87–1.47**	**.35**	25%	.25	\
		ICU death	3	1.27	0.68–2.36	.45	29%	.24	\
		In-hospital/28-day death	4	1.02	0.88–1.19	.76	0%	.45	\
		90-day death	\	\	\	\	\	\	\
	>0.5g/kg	*Overall analysis*	**6**	**1.02**	**0.85–1.22**	**.83**	20%	.28	\
		ICU death	1	0.84	0.42–1.66	.61	\	\	\
		In-hospital/28-day death	4	0.95	0.58–1.54	.83	36%	.19	\
		90-day death	3	1.19	0.98–1.43	.08	0%	.63	\
Type of control group	Other colloid	*Overall analysis*	**7**	**1.10**	**0.85–1.41**	**.47**	22%	.26	\
		ICU death	3	1.27	0.68–2.36	.45	29%	.24	\
		In-hospital/28-day death	5	1.01	0.87–1.18	.86	0%	.47	\
		90-day death	\	\	\	\	\	\	\
	Crystalloid	*Overall analysis*	**5**	**1.03**	**0.86–1.24**	**.72**	25%	.26	\
		ICU death	1	0.84	0.42–1.66	.61	\	\	\
		In-hospital/28-day death	3	1.04	0.55–1.97	.90	51%	.13	\
		90-day death	3	1.19	0.98–1.43	.08	0%	.63	\
Age	<60-year	*Overall analysis*	**6**	**1.02**	**0.89–1.18**	**.74**	0%	.78	\
		ICU death	1	0.35	0.02–8.08	.51	\	\	\
		In-hospital/28-day death	6	1.02	0.88–1.18	.79	0%	.51	\
		90-day death	2	1.22	0.78–1.91	.38	0%	.34	\
	>60-year	*Overall analysis*	**5**	**1.13**	**0.85–1.51**	**.40**	61%	.04	\
		ICU death	2	1.25	0.60–2.63	.55	66%	.08	\
		In-hospital/28-day death	2	1.64	0.30–8.83	.57	68%	.08	\
		90-day death	1	1.18	0.95–1.45	.13	\	\	\
MAP	<60 mm Hg	*Overall analysis*	\	\	\	\	\	\	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	\	\	\	\	\	\	\
		90-day death	\	\	\	\	\	\	\
	>60 mm Hg	*Overall analysis*	**5**	**1.03**	**0.86–1.24**	**.72**	24%	.26	\
		ICU death	2	0.84	0.50–1.43	.53	0%	.96	\
		In-hospital/28-day death	2	1.17	0.57–2.40	.67	69%	.07	\
		90-day death	2	1.20	0.99–1.46	.06	0%	.60	\

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Table 2

(***Continued***)

Category		Groups	No. studies	Effect estimate			Heterogeneity		Publication bias (Egger test)
				RR	95% CI	*P*	I^2	*P*	
Septic shock patients									
Type of human albumin	0.1% albumin	*Overall analysis*	\	\	\	\	\	\	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	\	\	\	\	\	\	\
		90-day death	\	\	\	\	\	\	\
	0.25% albumin	*Overall analysis*	**1**	**1.06**	**0.96–1.18**	**.26**	\	\	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	1	1.06	0.96–1.18	.26	\	\	\
		90-day death	\	\	\	\	\	\	\
	1% albumin	*Overall analysis*	**1**	**0.99**	**0.86–1.13**	**.86**	\	\	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	1	0.99	0.86–1.13	.86	\	\	\
		90-day death	\	\	\	\	\	\	\
	4% albumin	*Overall analysis*	**2**	**1.01**	**0.67–1.50**	**.97**	61%	.11	\
		ICU death	1	1.29	0.83–2.01	.25	\	\	\
		In-hospital/28-day death	1	0.85	0.66–1.09	.21	\	\	\
		90-day death	\	\	\	\	\	\	\
	5% albumin	*Overall analysis*	**6**	**0.99**	**0.84–1.15**	**.86**	0%	.55	\
		ICU death	1	0.92	0.76–1.10	.35	\	\	\
		In-hospital/28-day death	5	1.15	0.83–1.59	.39	0%	.73	\
		90-day death	\	\	\	\	\	\	\
	20% albumin	*Overall analysis*	**3**	**0.89**	**0.80–0.99**	*.03*	0%	.89	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	2	0.92	0.76–1.12	.41	0%	.91	\
		90-day death	1	0.87	0.77–0.99	*.03*	\	\	\
Dose of human albumin	<0.5g/kg	*Overall analysis*	**6**	**1.02**	**0.95–1.10**	**.57**	0%	.55	\
		ICU death	1	0.92	0.76–1.10	.35	\	\	\
		In-hospital/28-day death	5	1.04	0.96–1.13	.35	0%	.69	\
		90-day death	\	\	\	\	\	\	\
	>0.5g/kg	*Overall analysis*	**8**	**0.90**	**0.82–0.99**	*.03*	0%	.70	\
		ICU death	1	1.29	0.83–2.01	.25	\	\	\
		In-hospital/28-day death	6	0.91	0.79–1.06	.22	0%	.87	\
		90-day death	1	0.87	0.77–0.99	*.03*	\	\	\
Type of control group	Other colloid	*Overall analysis*	**7**	**1.05**	**0.97–1.13**	**.27**	0%	.77	\
		ICU death	\	\	\	\	\	\	\
		In-hospital/28-day death	7	1.04	0.96–1.13	.31	0%	.79	\
		90-day death	\	\	\	\	\	\	\
	Crystalloid	*Overall analysis*	**8**	**0.91**	**0.84–0.99**	*.02*	0%	.80	\
		ICU death	2	1.03	0.74–1.43	.87	52%	.15	\
		In-hospital/28-day death	5	0.93	0.80–1.06	.27	0%	.82	\
		90-day death	2	0.89	0.79–1.00	.06	0%	.32	\
Age	<60-year	*Overall analysis*	**6**	**1.01**	**0.94–1.09**	**.71**	0%	.74	\
		ICU death	1	0.92	0.76–1.10	.35	\	\	\
		In-hospital/28-day death	5	1.03	0.95–1.11	.48	0%	.89	\
		90-day death	\	\	\	\	\	\	\
	>60-year	*Overall analysis*	**8**	**0.91**	**0.82–1.00**	**.05**	0%	.45	\
		ICU death	1	1.29	0.83–2.01	.25	\	\	\
		In-hospital/28-day death	6	0.93	0.79–1.09	.34	0%	.56	\
		90-day death	1	0.87	0.77–0.99	*.03*	\	\	\
MAP	<60 mm Hg	*Overall analysis*	**2**	**0.92**	**0.78–1.08**	**.31**	0%	.91	\
		ICU death	1	0.92	0.76–1.10	.35	\	\	\
		In-hospital/28-day death	1	0.94	0.68–1.29	.68	\	\	\
		90-day death	\	\	\	\	\	\	\
	>60 mm Hg	*Overall analysis*	**5**	**0.90**	**0.81–1.00**	**.05**	0%	.46	\
		ICU death	1	1.29	0.83–2.01	.25	\	\	\
		In-hospital/28-day death	4	0.90	0.72–1.12	.36	0%	.61	\
		90-day death	1	0.87	0.77–0.99	*.03*	\	\	\

Italics represent P-value with statistical significance.

CI = confidence interval, MAP = mean arterial pressure, RR = risk ratios.

Meta-analysis showed that both low (RR = 1.05, 95%CI = 0.99–1.11, *P* = .11) and high (RR = 0.96, 95%CI = 0.89–1.03, *P* = .23) dose of human albumin cannot decrease the overall mortality (Table 2). The interaction was statistically significant among these 2 subgroups (I^2 = 72.5%, *P* = .06).

3.3.1.4. Subgroup analysis based on the type of control group. Fifteen RCTs' (n = 8415) control group were colloid[12,13,28–40] and 10 RCTs (n = 8429) were crystalloid.[9–11,28,41–46] Meta-analysis showed that human albumin group had a higher overall mortality than other colloid group (RR = 1.06, 95% CI = 1.00–1.13, *P* = .04), but

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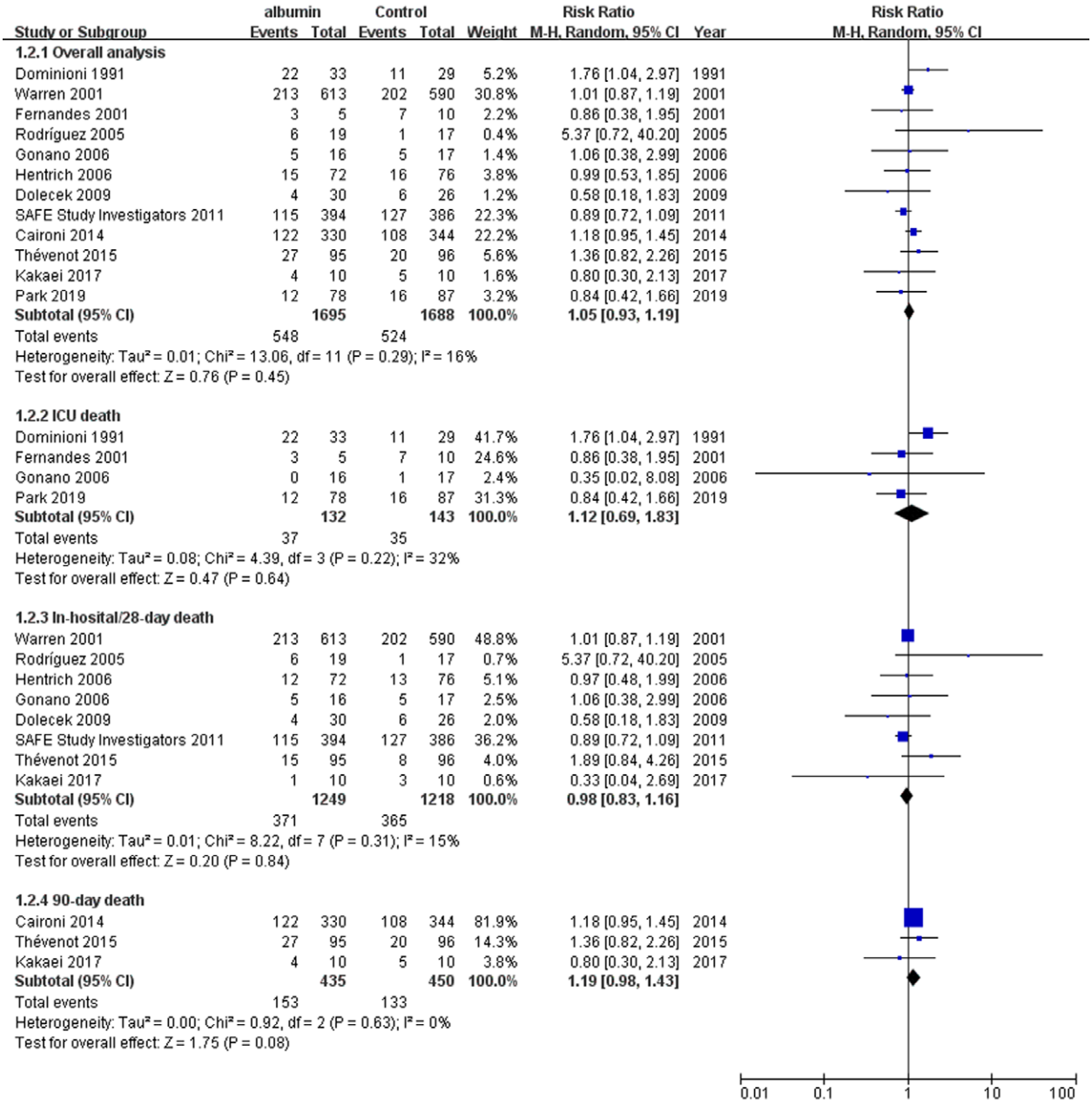

Figure 3. Forest plot showing the effect of human albumin treatment on overall, ICU, in-hospital/28-day, and 90-day mortality in sepsis patients. ICU = intensive care unit.

similar with crystalloid group (RR = 0.95, 95% CI = 0.89–1.02, $P = .16$) (Table 2). The interaction was statistically significant among these 2 subgroups ($I^2 = 82.4\%$, $P = .02$).

3.3.1.5. Subgroup analysis based on age. Thirteen RCTs (n = 9038) explored the effect of human albumin on the mortality of patients with age < 60 years[11,13,29,33,35–40,43,44,46] and 9 RCTs(n = 6519) with age > 60 years.[9,10,12,28,30,34,41,45] Meta-analysis showed that the mortality of human albumin group was similar with control group both in patients with age < 60 years (RR = 1.03, 95%CI = 0.98–1.09, $P = .23$) and age > 60 years (RR = 1.02, 95%CI = 0.89–1.16, $P = .78$) (Table 2). The interaction was not statistically significant among these 2 subgroups ($I^2 = 0\%$, $P = .58$).

3.3.1.6. Subgroup analysis based on MAP. Two RCTs (n = 408) explored the effect of human albumin on the mortality of patients with MAP < 60 mm Hg[11,46] and 10 RCTs (n = 1737) with MAP > 60 mm Hg.[9,10,12,28,32,37–39,43,45] Meta-analysis showed that the mortality of human albumin group was similar with control group both in patients with MAP < 60 mm Hg (RR = 0.92, 95%CI = 0.78–1.08, $P = .31$) and MAP > 60 mm Hg (RR = 0.99, 95%CI = 0.92–1.07, $P = .82$) (Table 2). The interaction was not statistically significant among these 2 subgroups ($I^2 = 0\%$, $P = .96$).

3.3.2. Sepsis patients.

3.3.2.1. Overall analysis. Twelve RCTs (n = 3383)[9,10,30,32–36,40,43–45] explored the effect of human albumin on the mortality of sepsis patients. Meta-analysis showed that human albumin cannot decrease the overall mortality of sepsis patients (RR = 1.05, 95% CI = 0.93–1.19, $P = .45$) (Fig. 3). The heterogeneity ($I^2 = 16\%$, $P = .29$) and publication bias ($P = .62$) were not significant among

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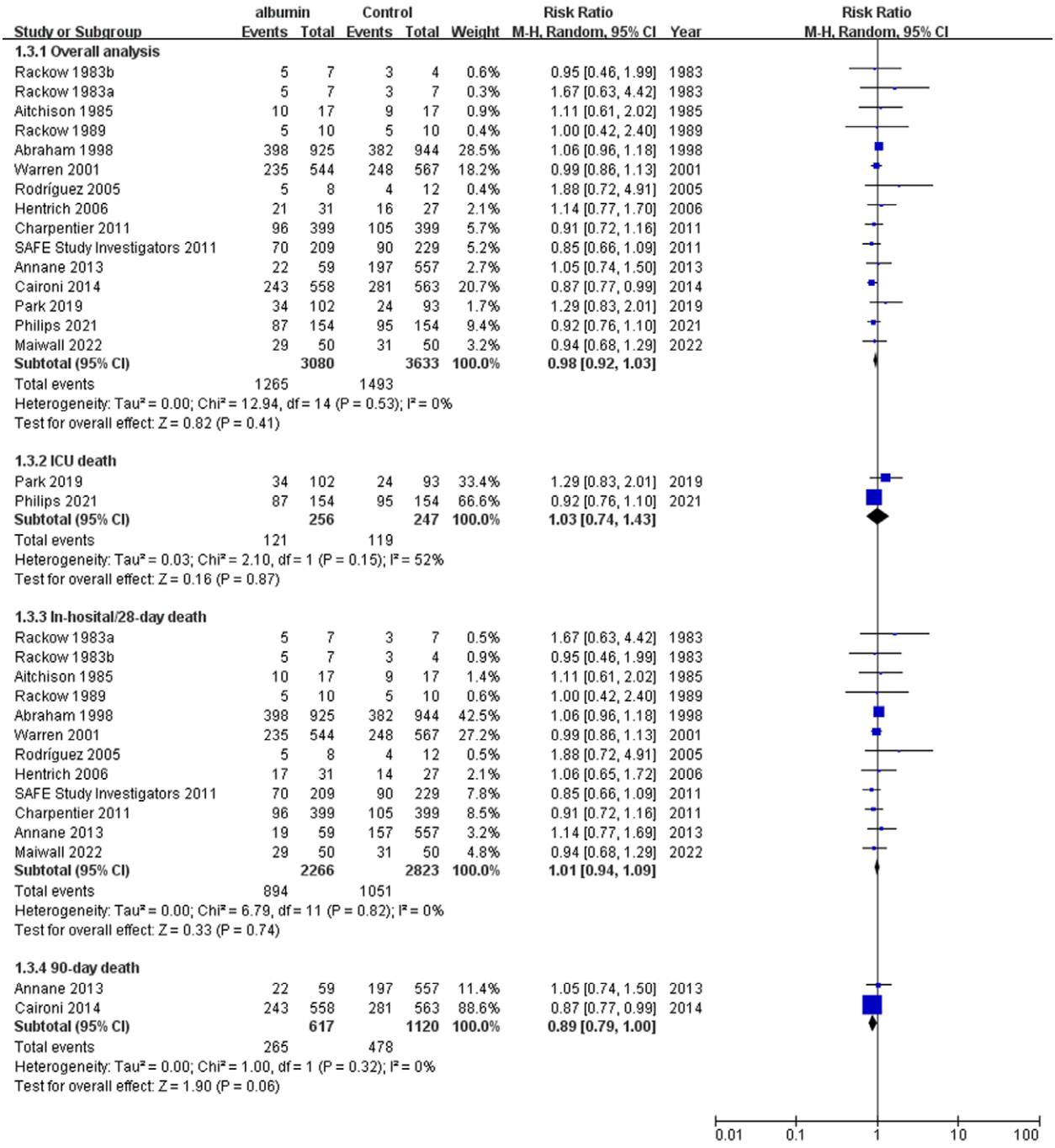

Figure 4. Forest plot showing the effect of human albumin treatment on overall, ICU, in-hospital/28-day, and 90-day mortality in septic shock patients. ICU = intensive care unit.

these studies. TSA indicated that the cumulative *Z* curve both did not cross conventional monitoring boundary for benefit and the trial sequential monitoring boundary (Fig. S3, Supplemental Digital Content, http://links.lww.com/MD/O232) suggesting that there was insufficient evidence to suggest the effect of human albumin in patients with sepsis. Given the potential bias of our study, further studies are needed to confirm whether albumin has an impact on mortality of patients with sepsis. Additionally, human albumin also cannot decrease the ICU (RR = 1.12, 95%CI = 0.69–1.83, *P* = .64), in-hospital/28-day (RR = 0.98, 95%CI = 0.83–1.16, *P* = .84), and 90-day (RR = 1.19, 95%CI = 0.98–1.43, *P* = .08) mortality of sepsis patients and none of them exhibited significant heterogeneity (Table 2).

3.3.2.2. Subgroup analysis based on the type of human albumin. Two RCTs' type of human albumin was 1% human albumin (n = 1236),[33,35] 2 were 4%[9,45] (n = 945), 4 were 5%[30,32,34,36] (n = 261), and 4 were 20%[10,40,43,44] (n = 941). Meta-analysis showed that human albumin cannot decrease the overall mortality of sepsis patients regardless of the type of human albumin used: 1% (RR = 1.02, 95%CI = 0.87–1.19, *P* = .84), 4% (RR = 0.88, 95%CI = 0.72–1.08, *P* = .22), 5% (RR = 1.31, 95%CI = 0.80–2.16, *P* = .29), or 20% (RR = 1.16, 95%CI = 0.96–1.40, *P* = .12), respectively (Table 2).

3.3.2.3. Subgroup analysis based on the dose of human albumin. Six RCTs (n = 1497) explored the effect of low dose

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of human albumin on the mortality of sepsis patients[30,32–36] and 6 RCTs (n = 1886) explored the high dose.[9,10,40,43–45] Meta-analysis showed that both low (RR = 1.13, 95%CI = 0.87–1.47, $P = .35$) and high (RR = 1.02, 95%CI = 0.85–1.22, $P = .83$) dose of human albumin cannot decrease the overall mortality of sepsis patients (Table 2).

3.3.2.4. Subgroup analysis based on the type of control group. Seven RCTs' (n = 1553) control group were colloid[30,32–36,40] and 5 RCTs' (n = 1830) were crystalloid.[9,10,43–45] Meta-analysis showed that human albumin group had a similar mortality of sepsis patients with other colloid group (RR = 1.10, 95%CI = 0.85–1.41, $P = .47$) or crystalloid group (RR = 1.03, 95%CI = 0.86–1.24, $P = .72$) (Table 2).

3.3.2.5. Subgroup analysis based on age. Six RCTs (n = 1651) explored the effect of human albumin on the mortality of sepsis patients with age < 60 years[33,35,36,40,43,44] and 5 RCTs (n = 1717) with age > 60 years.[9,10,30,34,45] Meta-analysis showed that the mortality of human albumin group was similar with control group both in patients with age < 60 years (RR = 1.02, 95%CI = 0.89–1.18, $P = .74$) and age > 60 years (RR = 1.13, 95%CI = 0.85–1.51, $P = .40$) (Table 2).

3.3.2.6. Subgroup analysis based on MAP. Five RCTs (n = 1825) explored the effect of human albumin on the mortality of sepsis patients with MAP > 60 mm Hg.[9,10,32,43,45] Meta-analysis showed that the mortality of human albumin group was similar with control group in patients with MAP > 60 mm Hg (RR = 1.03, 95%CI = 0.86–1.24, $P = .72$) (Table 2).

3.3.3. Septic shock patients.

3.3.3.1. Overall analysis. Fourteen RCTs (n = 6736) explored the effect of human albumin on the mortality of septic shock patients.[9–13,28,29,33,34,36,41,42,45,46] Meta-analysis showed that human albumin cannot decrease the overall mortality of septic shock patients (RR = 0.98, 95%CI = 0.93–1.04, $P = .57$) (Fig. 4). The heterogeneity ($I^2 = 0\%$, $P = .49$) and publication bias ($P = .22$) were not significant among these studies. TSA indicated that the diversity adjusted information size was 4424 which was less than that in our study (n = 6713) and the cumulative *Z*-curve surpassed the futility boundary, but it did not cross the trial sequential monitoring boundary for benefit or harm, indicating further studies are not required as they are unlikely to change the current conclusion (whether benefit or harm) (Fig. S4, Supplemental Digital Content, http://links.lww.com/MD/O232). Additionally, human albumin also cannot decrease the ICU (RR = 1.03, 95%CI = 0.74–1.43, $P = .87$), in-hospital/28-day (RR = 1.01, 95%CI = 0.94–1.09, $P = .74$), and 90-day (RR = 0.89, 95%CI = 0.79–1.00, $P = .06$) mortality of septic shock patients and none of them exhibited significant heterogeneity (Table 2).

3.3.3.2. Subgroup analysis based on the type of human albumin. One RCT's type of human albumin was 0.25% human albumin (n = 1869),[13] 1 was 1%[33] (n = 1111), 2 were 4%[9,45] (n = 633), 6 were 5%[11,12,28,34,36] (n = 420), and 3 were 20%[10,41,46] (n = 2019). Meta-analysis showed that human albumin infusion cannot influent the overall mortality of septic shock patients regardless of the type of human albumin used: 0.25% (RR = 1.06, 95%CI = 0.96–1.18, $P = .26$), 1% (RR = 0.99, 95%CI = 0.86–1.13, $P = .86$), 4% (RR = 1.01, 95%CI = 0.67–1.50, $P = .97$), or 5% (RR = 0.99, 95%CI = 0.84–1.15, $P = .86$), respectively. However, 20% human albumin can significantly decrease the overall mortality of septic shock patients (RR = 0.89, 95%CI = 0.80–0.99, $P = .03$) (Table 2).

3.3.3.3. Subgroup analysis based on the dose of human albumin. Six RCTs explored the effect of low dose of human albumin on the mortality of septic shock patients (n = 3400)[11,13,29,33,34,36] and 8 RCTs explored the high dose (n = 2686).[9,10,12,28,41,45,46] Meta-analysis showed that high dose of human albumin can significantly decrease the overall mortality of septic shock patients (RR = 0.90, 95%CI = 0.82–0.99, $P = .03$), but low dose cannot (RR = 1.02, 95%CI = 0.95–1.10, $P = .57$) (Table 2).

3.3.3.4. Subgroup analysis based on the type of control group. Seven RCTs' (n = 3126) control group were colloid[12,13,28,29,33,34,36] and 8 RCTs' (n = 3587) were crystalloid.[9–11,28,41,42,45,46] Meta-analysis showed that human albumin group had a significant lower overall mortality of septic shock patients than crystalloid group (RR = 0.91, 95%CI = 0.84–0.99, $P = .02$), but similar with other colloid group (RR = 1.05, 95%CI = 0.97–1.13, $P = .27$) (Table 2).

3.3.3.5. Subgroup analysis based on age. Six RCTs (n = 3480) explored the effect of human albumin on the mortality of septic shock patients with age < 60 years[11,13,29,33,36,46] and 8 RCTs (n = 2617) with age > 60 years.[9,10,12,28,34,41,45] Meta-analysis showed that the overall mortality of human albumin group was similar with control group both in patients with age < 60 years (RR = 1.01, 95%CI = 0.94–1.09, $P = .71$) and age > 60 years (RR = 0.91, 95%CI = 0.82–1.00, $P = .05$) (Table 2).

3.3.3.6. Subgroup analysis based on MAP. Two RCTs (n = 408) explored the effect of human albumin on the mortality of septic shock patients with MAP < 60 mm Hg[11,46] and 5 RCTs (n = 1799) with MAP > 60 mm Hg.[9,10,12,28,45] Meta-analysis showed that the overall mortality of human albumin group was similar with control group both in patients with MAP < 60 mm Hg (RR = 0.92, 95%CI = 0.78–1.08, $P = .31$) and MAP > 60 mm Hg (RR = 0.90, 95%CI = 0.81–1.00, $P = .05$) (Table 2).

3.4. Quality of evidence

The quality of evidence was summarized in Table S4, Supplemental Digital Content, http://links.lww.com/MD/O233.

4. Discussion

The current conventional meta-analyses of published RCTs suggest that human albumin cannot significantly improve the mortality in total septic patients. Previous meta-analyses[14–16,47] have examined the impact of albumin in resuscitating critically ill and/or septic patients, yet their conclusions have been varied. Such disparities could arise from variations in the target population, the type and dosage of human albumin administered, the selection of control groups, the duration of follow-up, and the number and reliability of the studies included. On the contrary, our meta-analysis suggests that human albumin may confer survival benefits for patients with septic shock, particularly when administered in the form of 20% human albumin at a daily dose exceeding 0.5 g/kg. Furthermore, compared to other colloid, our findings suggested that human albumin may significantly increase the mortality rate among septic patients overall, although this effect was not observed in subgroup analyses. In comparison to crystalloid, human albumin did not significantly decrease the mortality of total septic patients, but it did show a significantly decrease in septic shock patients.

Our study possesses several notable strengths. First, Delaney[14] and Patel[15] meta-analyses incorporated data from several retracted studies, primarily published by Boldt et al, potentially influencing the reliability of the results. In contrast, Xu,[16] Geng[47] and our study excluded these retracted studies. Second, previous meta-analyses might have included several unqualified RCTs. For example, the target population of Haupt RCT[48] was hypovolemic circulatory shock and Metildi RCT[49] was severe pulmonary insufficiency and they were not septic patients, but they were included to the all previous

meta-analyses.[14–16,47] Additionally, Heijden[50] and Trof[51] RCTs also involved non-septic critically ill patients and they were also included in Patel[15] meta-analysis. Third, the sample size of the current meta-analysis (24 RCTs; 10,869 patients) was larger than Delaney[14] (17 RCTs; 1977 patients), Patel[15] (18 RCTs; 4190 patients), Xu[16] (5 RCTs; 5838 patients), and Geng[47] (8 RCTs; 8606 patients) meta-analyses.

While our meta-analysis did not indicate a survival benefit from human albumin for septic patients, various potential mechanisms suggest its efficacy, particularly when compared with crystalloids. Besides intravascular volume expansion, human albumin helps maintain colloid osmotic pressure and capillary membrane permeability, inhibits platelet aggregation, and clears inflammatory factors and oxygen free radical.[52,53] These pathophysiological actions may play a crucial role sepsis progression.[54] It is noteworthy that subgroup analyses suggest potential benefits of human albumin for specific septic patients and at certain dosages, which aligns with a recent retrospective cohort study suggesting a reduction in mortality among septic patients with liver cirrhosis under specific conditions.[21] These findings not only provide the potential avenues for future research, but also support the individualized use of human albumin, thereby reducing the waste of medical resources.

Our meta-analysis gives clues to several important issues about the use of human albumin for septic patients. First, the optimal population of human albumin administration. Previous RCTs[9–11,46] and meta-analyses[15,16] explored the effects of human albumin on the survival of sepsis or septic patients, but the conclusions were controversial. Our meta-analysis suggested human albumin cannot significantly improve the survival of sepsis patients, but significantly improve the survival of septic shock patients in several settings, which major included high daily dose (>0.5g/kg) of human albumin. Second, the optimal concentration of human albumin administration. Xu cohort study showed that 5% human albumin had a significant lower 28-day mortality than 25% human albumin in total septic patients, which was similar with several studies regarding the critical ill patients.[55,56] Hu cohort study showed that both 5% and 25% human albumin can significantly decrease the 28-day mortality in patients with liver cirrhosis and sepsis.[21] Geng meta-analysis showed that 20% human albumin significantly better than 4% or 5% human albumin in the 90-day mortality of septic shock patients, but not in the 28-day mortality.[47] Our meta-analysis included more comprehensive type of human albumin (i.e., 0.1, 0.25, 1%, 4%, 5%, and 20%) and suggested that type of human albumin did not significantly influent the effect of human albumin on the 28-day mortality regardless of sepsis or septic shock patients. However, it was observed that 20% human albumin could significantly decrease the 90-day mortality in septic shock patients but not in sepsis patients. Third, the optimal timing of human albumin infusion. Unfortunately, no previous RCT explored the effect of timing of human albumin infusion on the survival of septic patients, but a recent cohort study suggested that human albumin significantly improved outcomes only when initiated in patients with a serum albumin level of 25 to 30 g/L.[21] However, the current meta-analysis cannot clarify this issue due to lacking the related data.

There are also several limitations of our meta-analysis. First, although we divided the control group into other colloid and crystalloid, the control group remains heterogeneous due to the different aims of each RCT. Second, because the age and MAP at baseline were not specified in every patient, we could not accurately stratify the patients into different subgroups. We should acknowledge that age and MAP at baseline were defined based on their clinical significance and preferences of each included study. Third, the daily dose of human albumin was estimated value, which was calculated by the total dose, duration of human albumin, and estimated patients' weight in each study. Thus, when we explored the effect of it on the mortality for different target population, results were potentially biased.

In conclusion, our meta-analysis doesn't support the generally use of human albumin in septic patients to improve the survival. Furthermore, well-designed RCTs are still needed to clarify the optimal populations and strategy for the use of human albumin in septic patients.

Author contributions

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